Schizophrenia Block

Adapted from the American Society for Clinical Psychopharmacology Model Curriculum

Learning Objectives

- Identify major target symptoms of schizophrenia treatment
- Become familiar with conventional & atypical antipsychotic medications
- Recognize major side effects of antipsychotic medications
- Recognize unique features of clozapine & depot antipsychotics

Outline

- Background about Schizophrenia
 - Dopamine Hypothesis
 - Dopamine Pathways
- Efficacy of Anti-psychotics
 - Treats agitation
 - Prevents relapse
 - Compliance, Medication dose & relapse
- Overview of an Antipsychotic Medication Trial
- Different Anti-psychotic medications
- Side effects of the Anti-psychotics
 - Common-EPS, TD, anti-cholinergic, metabolic syndrome,
 - Rare but serious-NMS
- Antipsychotic selection and treatment strategies algorithm

Dopamine Hypothesis of Schizophrenia

Dopamine Hypothesis

- Psychotic symptoms can be induced by dopamine agonists*
 - cocaine, amphetamines cause psychosis
- All anti-psychotics are dopamine antagonists
- Normal subjects-10% dopamine receptors occupied at baseline**
- Schizophrenic subjects-20% dopamine receptors occupied at baseline**

Major Dopamine Pathways

- 1. <u>Nigrostriatal tract</u>- (extrapyramidal pathway) substantia nigra to caudate nucleus & putamen of the basal ganglia
- 2. <u>Mesolimbic tract</u> midbrain tegmentum to nucleus accumbens & adjacent limbic structures
- 3. <u>Mesocortical tract</u> midbrain tegmentum to anterior cortical areas
- 4. <u>Tuberoinfundibular tract</u> arcuate & periventricular nuclei of the hypothalamus to the pituitary



Source: Hales RE, Yudofsky SC. *Textbook of Neuropsychiatry*. © 1987 American Psychiatric Press. Used with permission.

Dopamine Receptor Subtypes

D₁ Family

- D₁ and D₅ receptors
- Poor correlation with antipsychotic activity
- D₁ family may modulate effects of D₂ family

D₂ Family

- D₂, D₃, D₄ receptors
- High correlation with antipsychotic activity
- D₄ is prominent in limbic structures, but absent from extrapyramidal pathways
- Atypical antipsychotics have high D₄ affinity

Clinical Efficacy and Dopamine D₂ Blockade



Seeman P, Synapse 1987:1:133

1st Generation Antipsychotic: FGA's (Conventional/Neuroleptics)

High Potency

- Haloperidol (Haldol)
- Fluphenazine (Prolixin)
- Perphazine (Trilafon)
- Thiothixine (Navane)

Low Potency

- Chlorpromazine (Thorazine)
- Thioridazine (Mellaril)
- Mesoridazine (Serentil)



- How can anti-psychotics hit this therapeutic window?
 - Typical vs. Atypical

Kapur S & Remington G, Biol Psychiatry 2001;50:873

General Treatment Course Onset of effect of Anti-psychotics

- IM: peak plasma level, ~ 30 min
- PO: peak plasma level, ~ 1-4 hrs
- bioavailability IM > PO
 - PO, incomplete GI absorption, 1st pass effect
- 90% protein bound; unbound passes through blood brain barrier

Elimination Half-Times



Dopamine Hypothesis

- Psychotic symptoms can be induced by DA agonists*
 - cocaine, amphetamines cause psychosis

- All anti-psychotics are DA antagonists
- Antipsychotic's clinical efficacy correlates w/ D₂ blockade*
- Normal subjects-10% DA receptors occupied at baseline**
- Schizophrenic subjects-20% DA receptors occupied at baseline**
- ~30% pts no sig. response to anti-psychotic treatment
- Glutamate system dysfunction also linked to schizophrenia

*Carlsson A, Am J Psychiatry 1978;135:164; Seeman P, Synapse 1987:1:133 **Laruelle M, Quart J Nuc Med 1998;42:211

Dopamine D₂ Effects

Dopamine pathway		Effects
1.	Nigrostriatal tract	1.EPS: Dystonia, parkinsonism, akathisia.
		Tardive dyskinesia
2.	Mesolimbic tract	2. Antipsychotic effect
3.	Mesocortical tract	3. Negative type symptoms?
4.	Tuberoinfundibular tract	4. Endocrine changes:
		Prolactin elevation, galactorrhea, gynecomastia, menstrual changes, sexual dysfunction



% of D₂ receptors occupied by anti-psychotic effects efficacy alone or efficacy & EPS

 Shorter time of D₂ receptor occupancy is correlated with lower EPS

Efficacy of Antipsychotics

FDA Approved Indications for Antipsychotic Medications

Adults

- Schizophrenia (acute and maintenance)
- Bipolar disorder (acute mania, maintenance, bipolar depression)
- Agitation associated with schizophrenia or bipolar disorder

Children and Adolescents

- Schizophrenia
- Autism

Risperidone for Short-term Treatment



Marder SR & Meiback RC, Am J Psychiatry 1994;151:825

Olanzapine for Prevention of Relapse



Lieberman JA, et al. Am J Psychiatry 2003; 160:1396

Haloperidol for Long-term Prevention of Relapse



Hogarty GE & Goldberg, SC, Arch Gen Psychiatry 1973;28:54

Relationship between Medication Dose and Relapse

1 Year of Haloperidol Decanoate Treatment



Davis JM, et al., J Clin Psychiatry 1993;54(Suppl):24

Risperidone for Long-term Prevention of Relapse



Csernansky JG, et al., NEJM 2002;346:16

Neurocognitive Deficits

- Atypical antipsychotics have better cognitive profiles than conventional agents
- Atypical antipsychotics do not return cognitive functions to normal
- Neurocognitive benefits of atypical antipsychotics are of minor clinical significance

Injectable Olanzapine for Acute Agitation



Breier A, et al., Arch Gen Psychiatry 2002;59:441

Oral Risperidone vs IM Haloperidol for Acute Agitation



Currier GW & Simpson GM, J Clin Psychiatry 2001;62:153

Target Symptoms

- Active psychosis
 - most common reason for hospitalization
 - most responsive to medications
- Negative symptoms
 - poor response to medication
 - progress most rapidly during early acute phases of illness

Target Symptoms

- Cognitive impairment
 - may be improved or worsened by medications
- Functional deterioration
 - Highly correlated with cognitive symptoms
 - Moderately correlated with negative symptoms
 - Occurs mostly during acute episodes, which can be prevented by medications

Overview of Pharmacologic Treatment of Schizophrenia

Initial Medication Trial

Pharmacologic Treatment of Schizophrenia

- Psychopharmacology algorithms help structure the knowledge base that pertains to decision making
- Dosing strategies should be informed by the pertinent evidence base
- Anti-psychotic choice should be influenced by the patient's likely susceptibility to the common side effects

Anti-psychotic Algorithm

- Stage 1: SGA (2nd generation antipsychotic)
 - Partial or non-response?
- Stage 2: different SGA or FGA
 - Partial or non-response?
- Stage 3: Clozapine trial
- Stage 4: Clozapine + SGA or FGA
- Stage 5: New FGA or SGA
- Stage 6: 2 FGA's, 2 SGA's or FGA+SGA

Anti-psychotic Algorithm

- Stage 1: SGA (2nd generation antipsychotic)
 - Partial or non-response?
- Stage 2: different SGA or FGA
 - Partial or non-response?
- Stage 3: Clozapine trial
- Stage 4: Clozapine + SGA or FGA
- Stage 5: New FGA or SGA
- Stage 6: 2 FGA's, 2 SGA's or FGA+SGA

Adequate Anti-psychotic Trial

- FGA or SGA generation antipsychotic
 - At least 4 weeks of therapeutic dose
 - Full response? Continue dose
 - Partial response? Continue or $\rightarrow \uparrow$ dose
 - No response \rightarrow next step
 - 4 more weeks (8 weeks) repeat
 - 4 more weeks (12 weeks) may repeat, but should be able to decide

Speed of Response

- Speed of response
 - Not well understood
 - Clinical effects begin in the first week
- half life about 20 hours, steady state 4-7 days
- If patient does not achieve a 25% reduction in symptoms in the first 2 weeks, outcome is likely to be poor at 4 weeks (Leucht S: J Clin Psychiatry 2007)
- More improvement occurs in the first two weeks than the second two weeks (Leucht S: Biol Psychiatry 2007)

Adequate Anti-psychotic Trial

- First episode patients
 - Require lower antipsychotic dosing
 - Tend to have greater sensitivity to side effects

Anti-psychotic Algorithm

- Stage 1: SGA (2nd generation antipsychotic)
 - Partial or non-response?
- Stage 2: different SGA or FGA
 - Partial or non-response?
- Stage 3: Clozapine trial
- Stage 4: Clozapine + SGA or FGA
- Stage 5: New FGA or SGA
- Stage 6: 2 FGA's, 2 SGA's or FGA+SGA

Clozapine

• Requires more time

- 1st 4 weeks-initial titration of clozapine
- At least 12 weeks of therapeutic dose (16 weeks)
 - Full response? Continue dose
 - Partial response \rightarrow Assess serum level and adjust dose accordingly
 - No response \rightarrow Assess serum level and adjust dose accordingly
- 12 more weeks (28 weeks) -
 - Full response? Continue dose
 - Partial response → Assess serum level and adjust dose accordingly or consider next stage
 - No response \rightarrow consider next stage
- Effective for 30-50% of treatment-refractory patients
Clozapine for Long-term Treatment



Conley RR, et al., Am J Psychiatry 1999;156:863

Prevention of Suicide



Meltzer HY, et al., Arch Gen Psychiatry 2003;60:82

Clozapine

- Other considerations-when to use clozapine
 - Pts with recurrent suicidality or violence
 - Pts with substance abuse
 - Persistence of positive symptoms
 - if > 2 years-consider trial
 - if > 5 years-almost have to justify not doing a trial

Antipsychotic Medications

The Evolution of Antipsychotic Medications



Adapted from Lieberman J, et al., APA Annual Meeting, May 2001

Conventional or 1st Generation (FGA's) Antipsychotic Medications (Neuroleptics)

- Chlorpromazine (Thorazine) introduced in 1952; Several classes introduced in 1950s & 1960s
- Principal pharmacological activity: D₂ blockade
- Variable activity (side effects) at:
 - H_1 (histamine), M_1 (muscarinic), & α_1 (adrenergic) receptors
- High risk of Dopamine system side effects
 - EPS & Tardive Dyskinesia

Conventional or 1st Generation (FGA's) Antipsychotic Medications (Neuroleptics) Low Potency

- Lower EPS risk-(dopamine system side effects)
- Stronger anticholinergic (muscarinic) effects
- Most common agents
 - Chlorpromazine (Thorazine)
 - Thioridazine (Mellaril)
 - Mesoridazine (Serentil)

Conventional or 1st Generation (FGA's) Antipsychotic Medications (Neuroleptics)

High Potency

- High EPS risk-(dopamine system side effects)
- Weaker anticholinergic effects
- Most common agents
 - Haloperidol (Haldol)
 - Fluphenazine (Prolixin)
 - Perphazine (Trilafon)
 - Thiothixine (Navane)

- Bradykinesia (slow movements)
- Tremor
- Stiff, rigid muscles

- Dystonia (muscle spasms)
- Akathisia (subjective sense of restlessness)

- Akathisia (subjective sense of restlessness)
- Common
 - Prevalence ~20-30%
 - Most data obtained with FGA's
- Occurs early in treatment course
- Reversible, often treatment responsive

Treatment Options

- Reduce medication dose
- Slow down the rate of titration
- Consider alternative medication
- Adjunctive medication

Treatment – Adjunctive Medication

- Anticholinergic
 - Benztropine 1-2 mg bid-qid
 - Trihexyphenidyl 2-5 mg bid-qid
- Antihistamine
 - Diphenhydramine 25-50 mg bid-qid
- Dopaminergic
 - Amantadine 100 mg bid-tid

- Adverse reaction to antipsychotic medications
- Irregular, choreoathetotic movements
 - Chorea irregular, spasmodic movements
 - Athetosis slow writhing movements
- May occur in any muscle group
- Most common in facial, oral, and truncal muscles

Cumulative Incidence of TD with Conventional Antipsychotics



Natural History

- May spontaneously improve, remain static, or worsen
 - Static symptoms are most common
 - Spontaneous improvement is least common
- About half of patients experience relief of symptoms within 3 months of antipsychotic discontinuation

Acute Treatment

- Increase antipsychotic dose temporarily suppresses symptoms
- Benzodiazepine my bring about a modest reduction in symptoms

Maintenance Treatment

- Reduce antipsychotic dose and time of exposure
- Clozapine (standard dose)
 - 50% of patients show 50% reduction in movements
- Other treatments have not consistently been effective
 - Vitamin E Benzodiazepine
 - Dopaminergic agents

Branched-chain amino acids

Risk by class of medication

- High-potency conventional neuroleptic (20-40%)
- Low-potency conventional neuroleptic
- Paliperidone/Risperidone
- Aripiprazole/Olanzapine/Ziprasidone
- Quetiapine/Clozapine

Risk

Risk by class of medication:

- High potency conventional neuroleptic (7%/yr)
 - Low potency conventional neuroleptic (5%/yr)
 - Paliperidone/Olanzapine/Risperidone/Ziprasidone (0.5%/yr)
 - Quetiapine/Aripiprazole (uncertain)
 - Clozapine (none reported)

Risk

TD Incidence in Older Patients: Haloperidol versus Risperidone (1mg/d)



Cumulative Incidence of Persistent TD With Quetiapine in Elderly Psychosis Patients



Jeste DV, et al., Am Assoc Geriatric Psychiatry poster, 2000

Cumulative Annual Risk of Tardive Dyskinesia

	Age 20	Age 70
Conventional Neuroleptic	5%	30%
Atypical Antipsychotic	0.5%	2.5-5%

Kane JM, et al., J Clin Psychopharmacol 1988;8:52S. Chakos MH, et al., Arch Gen Psychiatry 1996;53:313. Woerner MG, et al., Am J Psychiatry 1998;155:1521. Correll CU, et al., Am J Psychiatry 2004; 161:414. Glazer WM, J Clin Psychiatry 2000; 61 suppl 4:21.

Conventional or 1st Generation (FGA's) Antipsychotic Medications: High Potency

- Advantages
 - Injectable formulations (including IV)
 - Depot formulations (Haldol & Prolixin)
 - Inexpensive
- Disadvantages
 - High risk of Dopamine system side effects
 - EPS & Tardive Dyskinesia

Conventional or 1st Generation (FGA's) Antipsychotic Medications: Low Potency

- Advantages
 - Highly sedating
 - Injectable formulations
 - Inexpensive
- Disadvantages
 - Highly sedating
 - Risk of qTc prolongation
 - Risk of tardive dyskinesia

The Evolution of Antipsychotic Medications



Adapted from Lieberman J, et al., APA Annual Meeting, May 2001

Atypical Antipsychotics (Second Generation Antipsychotics-SGA's)

- Developed on the basis of receptor activity in addition to D₂ blockade
- Less Dopamine system side effects
 - •Less EPS and Tardive Dyskinesia
- Broader spectrum of activity
 - Some benefit for negative & cognitive symptoms
- Beneficial for treatment-refractory patients (clozapine only)

Atypical Antipsychotics-SGA's

- Aripiprazole (Abilify)
- Risperidone (Risperdal)
- Paliperidone (Invega)
- Ziprasidone (Geodon)
- Asenapine (Saphris)
- Quetiapine (Seroquel)
- Olanzapine (Zyprexa)
- Clozapine (Clozaril) Second-line use only

Aripiprazole (Abilify)

- Advantages
 - Unique pharmacology (partial agonist)
 - Disintegrating tablet & injectable formulations
 - Long half-life
 - 15 mg superior to 30 mg; no advantage to \uparrow dose
 - Minimal risk of metabolic syndrome
- Disadvantages
 - Unpredictable response when combined with dopamine antagonists (what would you predict?)
 - Moderate-high cost
 - Akathesia

*

Risperidone (Risperdal)

- Advantages
 - Extensive clinical experience
 - Liquid, disintegrating tablet, & depot preparations
 - Relatively low cost
- Disadvantages
 - Dopamine system side effects
 - Dose-dependent EPS & Prolactin elevation
 - Moderate risk of weight gain

Paliperidone (Invega)

- •••----
 - Advantages
 - Does not require hepatic metabolism
 - Extended-release formulation: Invega Sustenna, monthly
 - 80% renally excreted; use in pts with liver disease
- Disadvantages
 - Dopamine system side effects
 - Dose-dependent EPS & Prolactin elevation
 - Moderate risk of weight gain
 - Avoid if pt has impaired renal clearance capacity
 - Limited clinical experience

Ziprasidone (Geodon)

- ----
 - Advantages
 - Low risk of weight gain or sexual dysfunction
 - Relatively low cost
 - Injectable formulation
 - Disadvantages
 - Twice-daily dosing with meals
 - qTc prolongation
 - Avoid if EKG shows qTc >500 milliseconds
 - Is pt on meds that may prolong qTc (TCA, quetiapine, thioridazine, foxacins) re-check EKG
 - Check pulse. Low pulse risks Torsades. Is pt on a drug that lowers pulse? (Beta-blocker?)

Quetiapine (Seroquel)

- Advantages
 - Lowest EPS risk
 - Sustained Release formulation-take once daily
 - Rapid onset of action
 - Sedating, but may cause insomnia
- Disadvantages
 - Longer dose titration (9 days to max dose?)
 - Moderate risk of weight gain
 - Moderate-high cost

Olanzapine (Zyprexa)

- Advantages
 - Extensive clinical experience
 - Superior retention in maintenance treatment (CATIE)
 - Disintegrating tablet and injectable forms
- Disadvantages
 - High risk of weight gain and metabolic syndrome
 - 30% pt $\uparrow >7\%$ body weight
 - ↑ triglycerides, ↑ lipids, ↑ HgbA1C; ↑ risk diabetes
 - Sedation
 - Liver irritation-be cautious in hepatitis pt or of pt on other meds that irritate liver (statins, depakote, carbamazepine, naltrexone)

Asenapine (Saphris)

- Advantages
 - New-will become clearer over time the benefits vs problems with this medication
- Disadvantages
 - New!! Yet to learn from non-drug company studies.
 - Risk of dopamine system side effects
 - EPS & TD
 - ↑ Prolactin
 - NMS
 - Orthostasis, hypotension, syncope, QTc prolongation,
 - Weight gain

Clozapine (Clozaril)

- Advantages
 - Effective for 30-50% of treatment-refractory patients
 - Suicidal risks, substance problems
 - Most effective for negative symptoms
 - Only proven treatment for TD
- Disadvantages
 - Risk of agranulocytosis
 - Weekly x 6 months, biweekly x 6 months, then monthly blood draws
 - Unfavorable side effect profile

Depot Antipsychotics

- FGA's
 - Haloperidol (Haldol) decanoate
 - Fluphenazine (Prolixin) decanoate
- SGA's
 - Risperidone depot (Risperdal Consta)
 - paliperidone palmitate (Invega Sustenna)
 - So far no evidence of better efficacy or safety than the FGA depot antipsychotics
Depot Antipsychotics

- Advantages
 - Ensured compliance
 - Underutilized in the US. Many pts are not as compliant as we think and do better with Depot
 - Lower total doses compared with oral medication may reduce side effects
- Disadvantages
 - Poor patient acceptance
 - Minimal flexibility in dosing

Side Effects

Common:

EPS, Tardive Dyskinesia; Metabolic Syndrome Uncommon but Serious: qTc; Increased Mortality in Elderly; NMS

Use of atypical antipsychotics is associated with metabolic dysregulation

- Weight gain
- Type 2 diabetes
- Elevated LDL cholesterol

- Elevated triglycerides
- Decreased HDL cholesterol
- Diabetic ketoacidosis

- Prevalence of obesity and diabetes in patients with schizophrenia is 1.5-2.0 times higher than the general population
- No studies on obesity and diabetes in drug-naïve schizophrenia patients are available

Risk of Metabolic Complications

Relative risk of medications

- Clozapine/Olanzapine/Low Potency FGA Neuroleptics
 - Paliperidone/Quetiapine/Risperidone/ High Potency FGA Neuroleptics
 - Aripiprazole/Ziprasidone

Risk

Meta-analysis of Antipsychotic-related Weight Gain Estimate at 10 Weeks^a



^a Quetiapine weight gain estimated at 6 weeks

Allison DB, et al., Am J Psychiatry 1999;156:1686

Metabolic Syndrome

Recommended monitoring for patients on atypical antipsychotics

	Baseline	4 wks	8 wks	12 wks	Quarterly	Annual	5 yrs
Personal/family history	Х					Х	
Weight (BMI)	Х	Х	X	Х	Х		
Waist Circumference	Х					Х	
Blood pressure	Х			X		Х	
Fasting plasma glucose	X			Х		Х	
Fasting lipid profile	Х			Х			X

ADA et al., Diabetes Care 2004; 27:596

Cardiovascular Adverse Events

- FGA low potency drugs thioridazine (Mellaril) & mesoridazine (Stelazine) are associated with qTc prolongation & increased risk of cardiac death
- Ziprasidone carries a "bold" warning regarding qTc prolongation & associated cardiac risk, but no increased incidence of cardiac mortality or morbidity has been detected with ziprasidone

Increased Mortality

- All atypical antipsychotics carry a "black box" warning of increased mortality in elderly patients with dementia-related psychosis
- Risk is comparable among all conventional and atypical antipsychotics

Increased Mortality



Schneider LS, et al., JAMA 2005; 294:1934

Increased Mortality

Retrospective study of mortality in 22,890 elderly patients receiving antipsychotics

- Higher risk with FGA antipsychotics OR = 1.37
- Higher risk with recent initiation of medicine
- Higher risk with higher doses

Side Effects - Overview

	EPS	Prolactin	Anticholinergic Symptoms	Orthostatic Hypotension	
			(Muscarinic)	(Adrenergic)	
Aripiprazole	+/-	+/-	+/-	+/-	
Clozapine	0	+/-	+++	+++	
High-potency FGA	+++	++	+/-	+	
Low-potency FGA	++	++	∔ .∔.+	+++	
Olanzapine	+/-	+/-	+	+/-	
Quetiapine	+/-	+/-	++	++	
Risperidone	+	++	+/-	+	
Paliperidone	+	++	+/-	+	
Ziprasidone	+/-	+/-	+/-	+/-	

Side Effects - Overview

	qTc Prolongation	Sedation (Histamine)	Weight Gain*	
Aripiprazole	+/-	+/-	+/-	
Clozapine	+	+++	+++	
High-potency FGA	+/-	+	+	
Low-potency FGA	++	+++	+++	
Olanzapine	+/-	++	+++	
Quetiapine	+/-	+++	++	
Risperidone	+/-	+	++	
Paliperidone	+/-	+	++	
Ziprasidone	+	+/-	+/-	

*ADA et al., Diabetes Care 2004;27:596

Neuroleptic Malignant Syndrome

- Incidence 0.2%
 - Estimated by combining data from published studies
- Dx criteria

- D₂-blockers use in past 30 days
 - 1 of 6 develop NMS within 24 hours of D₂ exposure
 - 4 of 6 within 1 week
 - Nearly all within 30 days

D₂-blockers

- Typical anti-psychotics
- Atypical anti-psychotics
- Anti-emetics:

- Pro-peristaltic agents:
- Anesthetics:
- Sedatives:

Prochlorperazine (Compazine) Metocloperamide (Reglan) Droperidol (Innovar) Promethizine (Phenergan)

NMS Dx Criteria

- 1. D_2 -blockers
- 2. Hyperthermia
- 3. Muscle rigidity
- 4. 5 of the 9 following symptoms
- 5. R/O other hyperthermia causes

No use in past 30 days

>38 C

↑HR, ↑ & ↓ BP, ↑RR/hypoxia,
↑CPK, metabolic acidosis, tremor,
incontinence, ↑ WBC,
diaphoresis/sialorrhea,

Neuroleptic Malignant Syndrome

• Treatment

- Stop d₂-blocker
- Supportive treatment-iv fluids, anti-pyretic, monitoring
- No consensus on other treatment options
 - Lorazepam (Ativan)-useful in reversing catatonia
 - Amantadine (Symmetrel)-may release dopamine from terminals
 - Bromocriptine (Parlodel)- d₂-agonist
 - Dantrolene (Dantrium)-causes direct muscle relaxation
 - ECT

NMS Dx Criteria

- Mortality rate
 - Once 20-30%, now estimated at 5-12%
 - Good prognosis, especially if
 - No rhabdomyolysis, renal failure, or aspiration pneumonia
- Post NMS
 - 30% risk of recurrent NMS with restarting d₂-blocker, but most patients can be safely restarted with precautions

Antipsychotic Treatment Selection Summary

Treatment Selection with SGA's

- All first-line SGA's are effective against psychotic symptoms
- All first-line SGA's are equally well tolerated in large studies
- Each medication has unique side effects
- Each medication has unique pharmacokinetics
- Individual patients may respond preferentially to the medications

Treatment Recommendations

- Continuous, full-dose antipsychotic treatment is the key to good outcome in schizophrenia
- "Lowest effective dose" strategies are associated with higher relapse rates and poorer outcomes

Antipsychotic Augmentation Strategies

- Augmentation strategies have generally shown modest results
- No one strategy is generally accepted
 - Mood stabilizers
 - Benzodiazepines
 - Antidepressants
 - Antipsychotic combinations

• ECT

APA Practice Guideline, Am J Psychiatry 2004;161 (2:suppl):1

Antipsychotic Combinations

- 20-25% of patients receive more than one antipsychotic
- Few data are available on efficacy & safety of antipsychotic combinations
- Anecdotal accounts of specific combinations have not been supported by formal studies
- Pharmacologic justification is weak
- Side effects tend to be additive
- Costs are always additive

Relative Costs of Atypical Antipsychotic Medications

